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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/870,962	05/30/2001	Olga Bandman	PF-0614-2 DIV	5425

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EXAMINER
MURPHY, JOSEPH F

ART UNIT	PAPER NUMBER
1646	9

DATE MAILED: 04/09/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/870,962	BANDMAN ET AL.	
	Examiner	Art Unit	
	Joseph F Murphy	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *22 January 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *63-81* is/are pending in the application.

4a) Of the above claim(s) *66,69,71,72,75,80 and 81* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *63-65,67,68,70,73,74 and 76-79* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) *3* .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of Group IL in Paper No. 8, 1/20/2003 is acknowledged. The traversal is on the ground(s) that: (i) the methods of making the claimed antibody should be examined with the product claims because there would be no undue burden to search the additional claims; (ii) Applicant further argues that antibodies to all 9 presented sequences should be searched since there is no burden to search antibodies to all nine sequences, because all the sequences were searched in the parent cases; and that (iii) the Markush group is sufficiently few in number and closely related such that antibodies to all nine sequences should be searched. This is not found persuasive for the following reasons.

Regarding argument (i), Applicant's attention is directed to MPEP 808.02 which states that "Where the related inventions as claimed are shown to be distinct under the criteria of MPEP 806.05 (c-i), the examiner, in order to establish reasons for insisting upon restriction, must show by appropriate explanation one of the following: (A) Separate classification thereof; (B) A separate status in the art when they are classifiable together; (C) A different field of search." As set forth in the Restriction requirement of Paper No.7, 12/17/2002, Group IL is classified in class 530, subclass 387.1; Group LVIX is classified in class 435, subclass 7.1; Group LXVIII is classified in class 435, subclass 69.6. The separate classification established for each Group demonstrates that each distinct Group has attained recognition in the art as a separate subject for inventive effort, and also a separate field of search. Thus, the Restriction requirement is proper.

Regarding argument (ii), antibodies to SEQ ID Nos: 1-9 are independent and distinct, each from the other, because they are products which possess characteristic differences in

structure and function, and each has an independent utility, that is distinct for each invention which cannot be exchanged. Although all nine claims were searched in the parent cases, the databases that must be searched are large, and growing continuously. Thus, there is a burden on the Office to search multiple sequences that differ substantially in structure and function.

Regarding argument (iii) If the members of the Markush group are sufficiently few in number or so closely related that a search and examination of the entire claim can be made without serious burden, the examiner must examine all the members of the Markush group in the claim on the merits, even though they are directed to independent and distinct inventions. Broadly, unity of invention exists where compounds included within a Markush group (1) share a common utility, and (2) share a substantial structural feature disclosed as being essential to that utility. In the instant case, the structural differences of the amino acid sequences of SEQ ID NO: 1-9 demonstrate that the polypeptides do not share a common structural feature, and are independent and distinct as shown in the Restriction requirement of Paper No.7, 12/17/2002.

The requirement is still deemed proper and is therefore made FINAL. Claims 63-81 are pending. Claims 66, 69, 71-72, 75, 80-81 are withdrawn from consideration pursuant to 37 CFR 1.142(b). Claims 63-65, 67-68, 70, 73-74, 76-79 are under consideration.

Claim Objections

Claims 63-65, 67-68, 70, 73-74, 76-79 are objected to because of the following informalities: They contain limitations drawn to non-elected Groups. Appropriate correction is required.

Specification

The title of the invention is not descriptive. A new title is required that is clearly indicative of the invention to which the claims are directed. Applicant should restrict the title to the claimed invention.

Claim Rejections - 35 USC §§ 101, 112, first paragraph

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 73 is rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter. The claim is directed to a polyclonal antibody that is not isolated, thus this claim reads on a product of nature.

Claims 63-65, 67-68, 70, 73-74, 76-79 are rejected under 35 U.S.C. § 101 because they are drawn to an invention with no apparent or disclosed patentable utility. The instant application has provided a description of an isolated DNA encoding a protein, the protein encoded thereby, and an antibody to the encoded protein. The instant application does not disclose the biological role of this protein or its significance. The claimed invention is not supported by either a credible, specific and substantial asserted utility or a well-established utility. Novel biological molecules lack well-established utility and must undergo extensive

experimentation. Applicant is directed to the Utility Examination Guidelines, Federal Register, Vol. 66, No. 4, pages 1092-1099, Friday January 5, 2001.

It is clear from the instant specification that the PKH-5 polypeptide has been assigned a function because of its similarity to known proteins (Specification at 73). However, it is commonly known in the art that sequence-to-function methods of assigning protein function are prone to errors (Doerks et al.1998). These errors can be due to sequence similarity of the query region to a region of the alleged similar protein that is not the active site, as well as homologs that did not have the same catalytic activity because active site residues of the characterized family were not conserved (Doerks et al. page 248, column 3, fourth and fifth paragraphs). Inaccurate use of sequence-to-function methods have led to significant function-annotation errors in the sequence databases (Doerks et al. page 250, column 1, third paragraph). Furthermore, Brenner (1999, Trends in Genetics 15:132-133) argues that accurate inference of function from homology must be a difficult problem since, assuming there are only about 1000 major gene superfamilies in nature, then most homologs must have different molecular and cellular functions. Finally, Bork et al. (1996, Trends in Genetics 12:425-427) add that the software robots that assign functions to new proteins often assign a function to a whole new protein based on structural similarity of a small domain of the new protein to a small domain of a known protein. Such questionable interpretations are written into the sequence database and are then considered facts.

Neither the specification nor the art of record disclose any diseases or conditions associated with the function or expression of the PKH-5 protein, therefore, there is no "real

world" context of use for antibodies to the protein. Further research to identify or reasonably confirm a "real world" context of use is required.

The specification asserts several allegedly patentable utilities for the claimed antibody to the PKH-5 polypeptide. The Specification asserts that the nucleic acid encoding the PKH-5 polypeptide is expressed in peripheral blood lymphocytes and retina (Specification at 91) and that thus, compounds modulating the activity of PKH-5 polypeptide of the instant application can be used to treat certain diseases (Specification at 91). However, this asserted utility is not specific or substantial. The specification does not disclose diseases associated with altered PKH-5 activity. Significant further experimentation would be required of the skilled artisan to identify individuals with such a disease. Since this asserted utility is also not present in mature form, so that it could be readily used in a real world sense, the asserted utility is not substantial.

After complete characterization, antibodies to the PKH-5 protein may be found to have a patentable utility. This further characterization, however, is part of the act of invention and until it has been undertaken Applicant's claimed invention is incomplete. The instant situation is directly analogous to that which was addressed in *Brenner v. Manson,* 148 USPQ 689 (Sup. Ct., 1966), in which a novel compound which was structurally analogous to other compounds which were known to possess anticancer activity was alleged to be potentially useful as an antitumor agent in the absence of evidence supporting this utility. The court expressed the opinion that all chemical compounds are "useful" to the chemical arts when this term is given its broadest interpretation. However, the court held that this broad interpretation was not the intended definition of "useful" as it appears in 35 USC § 101, which requires that an invention must have either an immediately obvious or fully disclosed "real world" utility. The court held that:

"The basic quid pro quo contemplated by the Constitution and the Congress for granting a patent monopoly is the benefit derived by the public from an invention with substantial utility", "[u]nless and until a process is refined and developed to this point-where specific benefit exists in currently available form-there is insufficient justification for permitting an applicant to engross what may prove to be a broad field", and "a patent is not a hunting license", "[i]t is not a reward for the search, but compensation for its successful conclusion."

The instant claims are drawn to an antibody to an PKH-5 polypeptide that has an as yet undetermined function or biological significance. Until some actual and specific significance can be attributed to the protein identified in the specification as PKH-5, the instant invention is incomplete. In the absence of knowledge of the natural substrate or biological significance of this protein, there is no immediately obvious patentable use for it. To employ an antibody of the instant invention in the identification of substances which inhibit the proteins activity is clearly to use it as the object of further research which has been determined by the courts to be a non-patentable utility. Since the instant specification does not disclose a "real world" use for antibodies to the PKH-5 polypeptide, then the claimed invention is incomplete and, therefore, does not meet the requirements of 35 USC § 101 as being useful.

Claims 63-65, 67-68, 70, 73-74, 76-79 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Even if, *arguendo*, a patentable utility is found for antibodies to the PKH-5 protein, claims 63-65, 67-68, 70, 73-74, 76-79 are rejected under 35 U.S.C. 112, first paragraph, because the specification, does not reasonably provide enablement for an antibody which binds to a polypeptide comprising a naturally occurring amino acids sequence which is 90% identical to SDEQ ID NO: 5, or for an antibody which binds to a polypeptide comprising an immunogenic fragment of SEQ ID NO: 5. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with these claims.

The specification does not provide enablement for an antibody which binds to a polypeptide comprising a naturally occurring amino acids sequence which is 90% identical to SDEQ ID NO: 5, or for an antibody which binds to a polypeptide comprising an immunogenic fragment of SEQ ID NO: 5. Claims 41-43 are overly broad since insufficient guidance is provided as to which of the myriad of variant polypeptides to which the antibodies are directed will retain the characteristics of PKH-5 activity. See In re Wands, 858 F.2d at 737, 8 USPQ2d at 1404. The test of enablement is not whether any experimentation is necessary, but whether, if experimentation is necessary, it is undue. The factors considered to be relevant in the instant case are set forth below:

(1) the breadth of the claims - The claims are drawn to an antibody which binds to a polypeptide comprising a naturally occurring amino acids sequence which is 90% identical to SDEQ ID NO: 5, or an antibody which binds to a polypeptide comprising an immunogenic fragment of SEQ ID NO: 5.

(2) the nature of the invention - The instant invention is an antibody.

(3) the state of the prior art - Voet et al. (1990) teaches that a single Glu to Val substitution in the beta subunit of hemoglobin causes the hemoglobin molecules to associate with one another in such a manner that, in homozygous individuals, erythrocytes are altered from their normal discoid shape and assume the sickle shape characteristic of sickle-cell anemia, causing hemolytic anemia and blood flow blockages (pages 126-128, section 6-3A and page 230, column 2, first paragraph). The Voet reference demonstrates that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. It is also known in the art that a single amino acid change in a protein's sequence can drastically affect the structure of the protein and the architecture of an entire cell. Thus, the amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Since detailed information regarding the structural and functional requirements of the peptides are lacking, it is unpredictable as to which encoding variations, if any, meet the limitations of the claims.

(5) the level of predictability in the art - The Voet reference demonstrates the unpredictability of the protein art.

(6) the amount of direction provided by the inventor - Applicant has only taught antibodies to SEQ ID NO: 5. The amino acid sequence of a polypeptide determines its structural and functional properties, and predictability of which amino acids can be substituted is extremely complex and well outside the realm of routine experimentation, because accurate predictions of a polypeptide's structure from mere sequence data are limited. Applicants do not disclose any

actual or prophetic examples on expected performance parameters of any of the possible variations of PKH-5.

(7) the existence of working examples – No working examples are provided.

(8) the quantity of experimentation needed to make or use the invention based on the content of the disclosure. As demonstrated by the Voet et al. reference, it is known in the art that even single amino acid changes or differences in the amino acid sequence of a protein can have dramatic effects on the protein's function. Since the claims encompass variant polypeptides, and fragments of polypeptides, and given the art recognized unpredictability of the effect of mutations on protein function, it would require undue experimentation to make and use the claimed invention.

Given the breadth of claims 63-65, 67-68, 70, 73-74, 76-79 in light of the predictability of the art as determined by the number of working examples, the level of skill of the artisan, and the guidance provided in the instant specification and the prior art of record, it would require undue experimentation for one of ordinary skill in the art to make and use the claimed invention.

Claims 63-65, 67-68, 70, 73-74, 76-79 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. Applicant is directed to the Guidelines for the Examination of Patent Applications Under the 35 U.S.C. 112, ¶ 1 "Written Description" Requirement, Federal Register, Vol. 66, No. 4, pages 1099-1111, Friday January 5, 2001.

These are genus claims. The claims are drawn to an antibody which binds to a polypeptide comprising a naturally occurring amino acids sequence which is 90% identical to SDEQ ID NO: 5. The claims also encompass an antibody that binds to a polypeptide comprising an immunogenic fragment of SEQ ID NO: 5. The scope of the claim includes numerous structural variants, and the genus is highly variant because a significant number of structural differences between genus members is permitted. The claims encompass antibodies directed to variant polypeptides, and fragments of polypeptides, and the art recognizes the unpredictability of the effect of mutations on protein function. The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features of the claimed genus of antibodies to polypeptides. There is no description of the conserved regions which are critical to the structure and function of the genus claimed. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. Structural features that could distinguish the compounds in the genus from other seven transmembrane region compounds are missing from the disclosure. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the antibodies to polypeptides

encompassed: there is no guidance in the art as to what the defining characteristics of the polypeptides might be. Thus, no identifying characteristics or properties of the instant antibodies are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Structural features that could distinguish compounds in the genus from others in the protein class are missing from the disclosure. No common structural attributes identify the members of the genus. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Since the disclosure fails to describe the common attributes or characteristics that identify members of the genus, and because the genus is highly variant, one of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, applicant was not in possession of the claimed genus.

Claim 63 sets forth the limitation that the claimed antibody must be directed to naturally occurring amino acid sequence which having protein kinase activity. However, in University of California v. Eli Lilly, 119 F.3 at 1568, 43 USPQ2d at 1406. the Court decided that a definition by function alone "does not suffice" to sufficiently describe a biomolecule "because it is only an indication of what the gene does, rather than what it is." Further, "it is only a definition of a useful result rather that a definition of what achieves that result...The description requirement of the patent statute requires a description of an invention, not an indication of a result that one might achieve if one made that invention". *Vas-Cath Inc. V. Mahurkar*, 19 USPQ2d 1111, clearly states that "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession *of the invention*. The invention is, for

purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117). The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (*See Vas-Cath* at page 1116).

The application on page 16, lines 20-34 sets forth a method of obtaining a PKH-5, variant or derivative that retains protein kinase activity. However, in Amgen Inc. v. Chugai Pharmaceutical Co., 927 F.2d 1200, 1206, 18 USPQ2d 1016 at 1022 it was held that "when an inventor is unable to envision the detailed constitution of a gene so as to distinguish it from other materials, as well as a method for obtaining it, conception has not been achieved until reduction to practice has occurred, i.e. until after the gene has been isolated". While Applicant has set forth a method for obtaining a PKH-5 naturally occurring variant which retains protein kinase activity, Applicant has not set forth within the claim the detailed constitution of the PKH-5 naturally occurring variant which retains protein kinase activity, and thus does not satisfy the written description requirement.

Claim Rejections - 35 USC § 112 second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 63-65, 67-68, 70, 73-74, 76-79 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 63 and 65 are indefinite in the recitation of the term "naturally occurring". It is unclear whether this term imposes a required limitation on the claim, such that it only encompasses, for example, polynucleotides amplified from human cDNA, or only sequences

produced by digestion with restriction enzymes of DNA isolated from tissue which contains polynucleotides encoding the polypeptide, or if the claim encompasses all polynucleotide sequences that encode the polypeptide. Therefore, the metes and bounds of the claim are unclear. Claims 64, 67-68, 70, 73-74, 76-79 are rejected due to their dependence on claims 63 and 65.

Conclusion

No claim is allowed.

Advisory Information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Joseph F. Murphy whose telephone number is 703-305-7245. The examiner can normally be reached on M-F 7:30-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Yvonne Eyler can be reached on 703-308-6564. The fax phone numbers for the organization where this application or proceeding is assigned are 703-305-3014 for regular communications and 703-308-0294 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

Joseph F. Murphy, Ph. D.
Patent Examiner
Art Unit 1646
April 1, 2003

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